CLINICAL TRIALS UPDATE

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Claudication: Exercise vs Endoluminal Revascularization (CLEVER) study update

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The Claudication: Exercise vs Endoluminal Revascularization (CLEVER) Study is a prospective multicenter randomized clinical trial designed to compare the relative clinical and cost-effectiveness of invasive revascularization with stents to supervised exercise rehabilitation in a cohort with moderate to severe claudication due to aortoiliac insufficiency. The study is currently enrolling at twenty-eight sites in the US and Canada. Enrollment of 217 participants is planned, with data collected at baseline, six months, and 18 months. The primary study endpoint is maximum walking duration (MWD) on a graded treadmill test; secondary endpoints include community-based walking, markers of cardiovascular disease risk (body mass index, waist circumference, blood pressure, lipid profile, glucose tolerance, and plasma fibrinogen), health-related quality of life, and cost effectiveness. There are currently sixty randomized participants; recruitment is projected to end in July 2010 and final study results reported in June 2012. (J Vasc Surg 2009;50:942-5.)

The Claudication: Exercise vs Endoluminal Revascularization Study (CLEVER) is a National Institutes of Health-sponsored partially blinded prospective, multicenter randomized clinical trial that tests the hypothesis that stent placement results in improved exercise treadmill test performance compared with supervised exercise rehabilitation for people with claudication due to aortoiliac insufficiency.[1] Data are collected at baseline, six months, and 18 months. There are multiple secondary endpoints, including measurement of community-based walking using pedometers, physiological variables associated with coronary heart disease risk (body mass index, waist circumference, blood pressure, lipid profile, glucose tolerance, C-reactive protein, and fibrinogen), health-related quality of life, and cost effectiveness.[1] The rationale for the study is that although stent-based revascularization may achieve arterial patency and improve symptoms, it is a local treatment for a systemic disease that may or may not improve community-based walking and patient satisfaction and whose relative efficacy and durability compared with exercise training is not established. Increasing activity levels is proven to be important to lower rates of myocardial infarction and stroke. Supervised exercise rehabilitation, supported by provision of exercise-focused behavioral medicine component in CLEVER, is designed to improve claudication symptoms and walking ability. Improved walking ability and activity levels may result in weight loss, improved blood pressure and lipid profiles, improved glycemic control, and fewer heart attacks, strokes, and cardiovascular-related deaths.

THE CLEVER STUDY TREATMENT PROGRAM

Study participants commit to an 18-month timeframe of participation, with data collected at baseline, six months, and 18 months. There are currently three treatment groups with asymmetric randomization including optimal medical care for 20% of patients (instructions to perform home exercise), supervised exercise rehabilitation (three times a week for six months with 12 months follow-up with a behavioral intervention) for 40% and aortoiliac stent placement for 40%. A combined stent plus supervised exercise

*See Appendix 1 for CLEVER Investigators.

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treatment arm, included for exploratory analyses, has been discontinued. All study participants receive cilostazol as a background claudication therapy throughout the course of their participation in the study, as long as the medication is well-tolerated, since cilostazol has been proven to improve walking ability in those with claudication.[2] Exercise sessions for individuals in this group are provided three times a week for one hour per session. Upon completing supervised exercise, the participant is contacted by a health educator, who begins a program of regular contact designed to foster adoption of regular exercise between six and 18 months. A combined stent plus supervised exercise treatment group, originally included as an exploratory analyses of this potential additive or synergistic benefit, has been discontinued so that recruitment could be focused on the primary study endpoints.

For all study participants, anatomic eligibility is determined by arterial imaging studies and/or by use of noninvasive tests without regard to "anatomic suitability" for revascularization by stent or TransAtlantic InterSociety Consensus (TASC) classification of the lesion. A secondary recruitment and treatment plan that would expand study inclusion to participants with only femoropopliteal artery stenoses[1] was considered as a potentially important expansion of the CLEVER study goals to a particularly relevant contemporary symptomatic PAD cohort. However, inclusion of this expanded study population was not activated due to concerns that aorto-iliac and femoropopliteal revascularization might be associated with differential relative treatment effects. American College of Sports Medicine and American Heart Association/American College of Cardiology (AHA/ACC) exclusions for individuals who could not reliably undergo exercise training and exercise testing, respectively, are also utilized (Table I, online only).

ENROLLMENT AND STUDY TIMELINE: LESSONS FOR THE VASCULAR HEALTHCARE COMMUNITY

There are currently twenty-eight active enrollment centers in CLEVER (Table II, online only), and current plans are to activate as many as 30 US sites and four Canadian sites. As of April 2009, there are 60 participants enrolled. Slow recruitment has been often observed in "strategy of care" randomized trials.[3] Nevertheless, since the study does not use a time-to-event endpoint, slow recruitment does not affect study power and the sponsor, the National Heart, Lung, and Blood Institute, is very committed to getting the important data the CLEVER will produce. Enrollment is scheduled to end in July of 2010, and given 18 months of follow-up, study results should be available by June 2012.

We note that a major component of the recently signed American Recovery and Reinvestment Act is money for increasing comparative effectiveness research, with one of the studies specifically mentioned being a comparison of invasive versus noninvasive treatment for people with ". . . leg pain that results from blockage of the arteries in the lower legs."[4] The treatment of PAD is extremely costly,[5] and the durability and effectiveness of current treatments needs to be demonstrated to ensure reimbursement in the future. Clearly the community of vascular healthcare professionals needs to participate more actively in multicenter randomized clinical trials like CLEVER, as do practitioners focused on other diseases such as cancer, heart disease, and infectious diseases, in order to acquire the knowledge of how best to manage the patients that they serve and to ensure reimbursement for their services. National Institutes of Health multicenter clinical trials of PAD will prove to be the most important PAD studies of our time and will validate care and payor policy well into the future.

POPULATION

Ascertainment of eligibility is satisfactory to date, with only one participant enrolled who was found to not have aortoiliac insufficiency but rather had femoropopliteal artery obstruction only. However, eligibility criteria were not followed correctly for this participant, but according to intention-to-treat principles they remain in their assigned treatment group. The population currently has an average age of 65.2 ± 9.5 years, has a 2:1 male predominance, and is approximately 20% ethnic minorities, with 37.5% reporting prior myocardial infarction, 23.4% with prior coronary artery revascularization, and 25% a history of diabetes mellitus.

PARTICIPANT FOLLOW-UP AND DATA COLLECTION

Compliance with the CLEVER study protocol has been satisfactory and well within assumptions made for power calculations. Four study participants have elected to withdraw from subsequent follow-up, and data compliance for participants remaining in the study is over 90%. Of the other 20 participants in the supervised exercise group, compliance with supervised exercise has been excellent, with subjects achieving an average of 72% attendance of a total of 78 (26 weeks, three times a week) exercise sessions scheduled for each participant. Since the study sample size was inflated by 30%, this high compliance with the study protocol and high rate of complete data collection demonstrates that CLEVER is likely to have sufficient power to definitively inform the primary study hypotheses on trial completion.

SAFETY

The CLEVER study compares treatment strategies that are based on known treatments that have low risk. CLEVER does not use any devices or drugs that are not approved by the U.S. Food and Drug Administration. The safety profile of the study has been excellent, with no unanticipated device or exercise-related adverse events, and only three significant adverse events observed, none felt to be related to a study treatment.

OUTCOMES

CLEVER has been designed to provide one planned interim data evaluation, which will occur after half of the study participants have completed their six-month follow-up visit. Subject compliance data do not suggest any clinically relevant outcome advantage or disadvantage for any treatment group. Acceptance of supervised exercise has

been high. We have also anecdotally observed improvements in exercise performance for all treatment groups. Whether this anecdotal experience will translate into a better relative treatment effect for any treatment group will await formal analysis.

CONCLUSIONS

CLEVER represents one of the most important randomized clinical trials that is designed to evaluate the clinical efficacy and risk of the three major claudication treatments, and is underway with 48 patients randomized as of February 2009. The only existing randomized clinical trials have demonstrated no benefit of treatment strategies that use only plain balloon angioplasty or arterial stents as compared with supervised exercise.[6,7] Payors including the federal government are demanding data to support reimbursement for medical services. Although all other aspects of study execution are satisfactory, subject recruitment in CLEVER has underperformed. Although this is common in treatment strategy trials,[3] it is particularly relevant for the vascular community that has long striven to have access to well-funded clinical trials. The CLEVER study provides a unique opportunity to provide important scientific evidence that will inform physicians and patients regarding optimal management of people with claudication, and we call on the vascular healthcare community to take an enlightened stance on this and other PAD treatment strategy trials, to embrace their role as scientists as well as clinicians, and to contribute in spirit and in fact to the successful completion of the CLEVER Study.

AUTHOR CONTRIBUTIONS

Conception and design: TM, AH, DC, JR, AC, EM, DC, JM
Analysis and interpretation: TM, AH, DC, JR, AC, EM, DC, JM
Data collection: TM, AH, DC, JR, AC, EM, DC, JM
Writing the article: TM, AH, DC, JR, AC, EM, DC, JM
Critical revision of the article: TM, AH, DC, JR, AC, EM, DC, JM
Final approval of the article: TM, AH, DC, JR, AC, EM, DC, JM
Statistical analysis: DC, JM, TM, AH
Obtained funding: TM, DC, AH, JM
Overall responsibility: TM

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Appendix. CLEVER Study lead investigators

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INVITED COMMENTARY

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Atherosclerotic peripheral arterial occlusive disease represents a significant burden; both to patients who carry the diagnosis and to the healthcare system. Claudication is simply one manifestation of a systemic process, and recognition of this fact has fueled comparative studies such as the Claudication: Exercise Versus Endoluminal Revascularization (CLEVER) trial, described by Murphy and colleagues, and updated in this issue of the Journal.[1] Any contemporary comparative effectiveness trial examining claudication should therefore focus not only on traditional measures of claudication, but on the systemic effects of atherosclerosis, and the economic sustainability of any proposed treatment strategy.

The rationale for the study is that anatomic-based treatment alone does not offer the same potential benefits afforded to systemic therapy, namely exercise therapy and medical optimization. High-profile trials have demonstrated the equivalence of systemic treatment to revascularization in the coronary vascular bed in many patient populations.[2] The non-interventional cohorts in the CLEVER study have the additive benefits of exercise therapy (supervised and non-supervised) and represent appropriately managed patients by contemporary standards. There are several obvious critiques to the trial setup, including anatomic restriction to the aortoiliac segment, lack of medical management followed by conditional interventional therapy (patients who fail conservative measures), and small sample size with restricted follow-up, which will limit the ability to observe the potential long-term benefits of sustained exercise therapy. Still, the collaborators are to be commended for executing a controlled claudication trial designed to address the systemic management of atherosclerosis.

The importance of randomized trials such as the CLEVER study in vascular disease management cannot be overstated. Endovascular treatments have undoubtedly lowered the morbidity of revascularization procedures, and benefited enumerable patients. However, the widespread adoption of endovascular therapy for the stable disease process of claudication has largely been advanced without rigorous trials and in many cases without proper attention to the medical management of the systemic disease process. However, with a renewed interest in cost effective healthcare, there is an avenue to reverse this trend.

Comparative effectiveness research has been embraced by the federal government, and in fact, funding has been set aside in the America Recovery and Reinvestment Act. In this setting, multicenter comparative trials such as this are essential to the process of data-driven healthcare reform. Equipped with randomized trial data, vascular providers will be able guide individual patient treatment, freed from anecdotal reports and marketing-driven presentations that support an array of untested procedures.

Furthermore, payors should have a keen interest in the cost-efficacy outcomes from this trial. Should supervised exercise therapy and medical optimization prove to be effective, there is a potential to change the landscape so that these services, which are not currently covered, become reimbursed. What more could vascular providers, patients, and society want other than to reimburse a therapy that treats the systemic risk factors for atherosclerosis and improves overall patient health?

Many critics of comparative effectiveness based care worry that its application will threaten the personal nature of the doctor-patient relationship.[3] There is this potential, but vascular surgeons, who are the only comprehensive providers of vascular care, should welcome the opportunity to have real scientific data upon which to recommend care to their patients, whether it be by medical, interventional, or surgical means. The challenge to our specialty will be to assume a prominent leadership role in trial design, conduct, and real-world implementation, so as to provide individualized, financially responsible, and scientifically-driven care.

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Table I (online only). CLEVER study eligibility criteria

Inclusion Criteria

1. Subject has symptoms suggestive of intermittent claudication, such as exercise-induced pain, cramps, fatigue, or other equivalent discomfort, involving large muscle groups of the leg(s) (calf, thigh, buttocks), relieved by rest.
2. Subject is ≥40 years old.
3. Claudication score consistent with "Rose," "atypical," or "noncalf" claudication by San Diego Claudication Questionnaire (see Appendix A for acceptable responses).
4. Positive noninvasive evaluation for significant aortoiliac PAD on the most symptomatic side(s) (bilaterally if symptoms are equal):
   a. Contrast arteriography: Contrast arteriogram showing at least 50% stenosis in the aorta, common iliac artery, or external iliac artery, OR
   b. Computed tomographic angiography (CTA) or magnetic resonance angiography (MRA): At least 60% stenosis in the aorta, common iliac artery, external iliac artery, accompanied by a biphasic or monophasic Doppler wave form at the common femoral artery (loss of early diastolic flow reversal or loss of forward flow during diastole), OR
   c. Duplex ultrasound: Occlusion or focal doubling of peak systolic velocity in the aorta, common iliac artery, or external iliac artery, accompanied by a biphasic or monophasic Doppler wave form at the common femoral artery (loss of early diastolic flow reversal or loss of forward flow during diastole), OR
   d. Vascular noninvasive physiologic tests: Ankle-brachial index ≤0.9 (or abnormal ankle pulse volume recording (PVR) waveform at ankle if arteries are incompressible*) with resting thigh-brachial index (thigh-BI) <1.1, and common femoral artery Doppler systolic acceleration time >140 msec [these tests may be ordered for study screening].
      *Abnormal PVR waveform must lack augmentation at the ankle, have a delayed, rounded systolic peak, and straight or convex downslope, and must be reviewed by the core lab.
      Note: MRA/CTA, and contrast arteriogram images images must be submitted to the Clinical Coordinating Center and Doppler waveform tracings to the Noninvasive Test Committee for over read pre- or post-randomization.
5. Highest ankle pressure reduced by at least 25 mm Hg after exercise compared to resting pressure (or loss of previously present Doppler signal for both the posterior tibial and anterior tibial arteries immediately after exercise if arteries were incompressible).

Note: The highest ankle pressure result is determined by using the higher result of either the dorsalis pedis or posterior tibial artery measurement.

6. Subject has moderate to severe claudication symptoms, defined as less than 11 minutes maximum walking duration (MWD) at baseline (initial) Gardner treadmill test (see Appendix B).
7. Performance on a second Gardner treadmill test within 25% of the initial baseline MWD test result.

Exclusion Criteria

1. Presence of critical limb ischemia (Rutherford Grade II or III12 PAD, defined as pain at rest, ischemic ulceration, gangrene) or acute limb ischemia (pain, pallor, pulselessness, paresthesias, paralysis) in either leg.
2. Common femoral artery (CFA) occlusion or ≥50% stenosis by angiography, MRA, CTA, or duplex ultrasound or doubling of systolic velocity in the ipsilateral common femoral artery by duplex ultrasound, or 50% diameter stenosis by visual estimate in the CFA by angiography, MRA, or CTA, (inadequate outflow for iliac stent intervention), if available pre-randomization.
3. Known total aortoiliac occlusion from the renal arteries to the common iliac arteries (all other occlusions ARE eligible).
4. Participant has bilateral claudication symptoms and the limb that is more symptomatic does not show evidence of aortoiliac insufficiency as described in inclusion criterion number 4.
5. Participant has bilateral claudication symptoms, but both limbs are equally symptomatic and one side does not show evidence of aortoiliac insufficiency as described in inclusion criterion number 4.
6. Subject meets the following exclusions based upon modified American College of Sports Medicine criteria for exercise training:
   i. Ambulation limited by co-morbid condition other than claudication, for example:
      1. Severe coronary artery disease
      2. Angina pectoris
      3. Chronic lung disease
      4. Neurological disorder such as hemiparesis
      5. Arthritis, or other musculoskeletal conditions including amputation
   ii. Poorly-controlled hypertension (SBP > 180 mm Hg).
   iii. Poorly-controlled diabetes mellitus.
   iv. Other active significant medical problems such as cancer, known chronic renal disease (serum creatinine >2.0 mg/dL within 60 days or renal replacement therapy), known chronic liver disease or anemia, active substance abuse, or known history of dementia.
7. Contraindication to exercise testing according to AHA/ACC guideline, specifically: Acute myocardial infarction (within 3-5 days), unstable angina, uncontrolled cardiac arrhythmias causing symptoms or hemodynamic compromise, active endocarditis, symptomatic severe aortic stenosis, acute pulmonary embolus or pulmonary infarction, acute noncardiac disorder that may affect exercise performance or be aggravated by exercise such as infection, thyrotoxicosis, acute myocarditis or pericarditis, known physical disability that would preclude safe and adequate test performance, known thrombosis of the lower extremity, known left main coronary stenosis or its equivalent, moderate stenotic valvular heart disease, electrolyte abnormalities, known pulmonary hypertension, tachyarrhythmias or bradyarrhythmias, hypertrophic cardiomyopathy, mental impairment leading to inability to cooperate, or high degree atrioventricular block.
8. Arterial insufficiency of target lesion due to restenosis of an angioplasty/stent or bypass is not eligible.
9. Recent (<3 months) infrainguinal revascularization (surgery or endovascular intervention).
10. Recent major surgery in the last 3 months.
11. Abdominal aortic aneurysm >4 cm or iliac artery aneurysm >1.5 cm is present.
12. Patients who are pregnant, planning to become pregnant, or lactating.
13. Unwilling or unable to attend regular (three times a week) supervised exercise sessions. {Please review this commitment carefully with each prospective participant}
14. Weight >350 lbs or 159 kg (may exceed treadmill and angiography table limits).

Table I (online only). Continued

15. Language barrier exists for primary Quality of Life instruments (available in English and Spanish).
16. Inability to understand and sign informed consent forms due to cognitive or language barriers (interpreter permitted).
17. Absolute contraindication to iodinated contrast due to prior near-fatal anaphylactoid reaction (laryngospasm, bronchospasm, cardiorespiratory collapse, or equivalent) and which would preclude patient from participation in angiographic procedures.
18. Allergy to stainless steel or nitinol.
19. Nonatherosclerotic cause of PAD (fibromuscular dysplasia, dissection, trauma, etc).
20. Inability to walk on a treadmill without grade at a speed of at least 2 mph for at least two minutes on the first treadmill test.
21. ST-segment depression >1 mm in any of the standard 12 electrocardiogram leads or sustained (>30 seconds) arrhythmia other than tachycardia or occasional premature atrial or ventricular contractions during exercise testing.
22. Post-exercise systolic blood pressure within the first five minutes after eligibility treadmill test lower than pre-exercise systolic blood pressure.
23. A peak heart rate >80% of maximum (calculated by subtracting age from 220) while reporting "onset" of claudication symptoms during the second baseline examination.
24. Repeat treadmill test shows an MWD result that is >25% different than the subject's initial Gardner treadmill test result.
25. Current active involvement in a supervised exercise program (eg, with a trainer, exercise protocol, and goals, such as in cardiac or pulmonary rehabilitation) for more than two weeks within the prior six weeks.

Table II (online only). Enrolling centers and site principal investigators (as of February 10, 2009)

Site	*Principal investigator*
Rhode Island Hospital, Providence, RI	Timothy Murphy, MD
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Vascular and Endovascular Specialists of Ohio, Mansfield, Ohio	William Miller, MD
Torrance Memorial Medical Center, Torrance, Calif	Mark Lurie, MD
Ochsner Clinic, New Orleans, La	Willie Chi, MD
VA Ann Arbor, Ann Arbor, Mich	Venkat Krishnamurthy, MD
Forsyth Medical Center, Winston-Salem, NC	Daniel Golwyn, MD
Providence Medical Research Center, Spokane, Wash	Stuart Cavalieri, MD
St. Joseph Hospital, Orange, Calif	Mahmood Razavi, MD
Stony Brook Hospital, Stony Brook, NY	Apostolos Tassiopoulos, MD
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VA Central Arkansas, Little Rock, Ark	Mahmoud Moursi, MD
VA Palo Alto, Palo Alto, Calif	Fritz Bech, MD
Oregon Health Sciences University, Portland, Ore	John Kaufman, MD
Iowa Clinic, Des Moines, Iowa	John Matsuura, MD
Mayo Clinic, Rochester, Minn	Audra Duncan, MD
Johns Hopkins Hospital, Baltimore, Md	Elizabeth Ratchford, MD
Methodist Hospital, Houston, Tex	Mark Davies, MD
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Rapides Regional Medical Center, Alexandria, La	William Long, MD
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